Standardised classification of the aetiology of bronchiectasis using an objective algorithm

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Dear editor,

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Variation in the assignment of aetiology impacts on every aspect of epidemiological research into bronchiectasis, as well as clinical trials where the inclusion of patients with post-infective or idiopathic bronchiectasis is only meaningful if we have standardised methods of assigning these aetiologies.(2) The aim of this study was to create a bronchiectasis aetiology classification algorithm that could be applied objectively to different healthcare settings. This algorithm was tested in a multicentre database of bronchiectasis patients with the goal of improving the degree of agreement and alignment between different centres.

An analysis of ten databases (Dundee, Edinburgh, Newcastle– United Kingdom; Haifa-Israel; Galway-Ireland; Leuven-Belgium; Athens-Greece; Monza-Italy; Barcelona-Spain; Serbia) of outpatients with BE was performed. Consecutive patients aged ≥18 years with a diagnosis of BE based on high-resolution computed tomographic scans were enrolled. Patients with cystic fibrosis or traction bronchiectasis due to pulmonary fibrosis were excluded. Local ethics committee approved the data collection at each site.

Demographics, previous medical history, comorbidities, as well as radiological, laboratory and microbiological findings were recorded. At each location, the aetiological diagnosis made by the clinician was also recorded. Centres all followed a standard of care that was consistent with the British Thoracic Society (BTS) 2010 guidelines in terms of testing for underlying causes.(3) The method of assignment of aetiologies and co-morbidities has been previously reported.(10)

An aetiological algorithm (figure 1-A) was generated based on the 2010 BTS guidelines. The initial assessment was required to have a documented evidence of BE in HRCT scan and a clinical history compatible with BE. All patients should then have completed a group of initial tests – complete blood count, protein electrophoresis, immunoglobulin levels (IgG, IgM, IgA, IgE), specific antibody levels (against tetanus toxoid, *S. pneumoniae* and *H. influenzae* type b), specific IgE and IgG/precipitins for *Aspergillus fumigatus*, bacterial and mycobacterial sputum culture and pulmonary function tests.(3)

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entities would be analysed. This group was classified as "Possible diagnosis" and included allergic bronchopulmonary aspergillosis (ABPA), post nontuberculous mycobacteria infection, post tuberculosis, chronic obstructive pulmonary disease (COPD) (defined as described in (9)), asthma, gastro-oesophageal reflux disease (GORD)/aspiration, and secondary immunodeficiency. If one of these diseases was the only possible aetiology present and if there were no atypical features, we also considered this a definitive diagnosis. If this was not the case or if the suspected aetiology was not in this group, we had to consider a final group of "diagnosis of exclusion" where in the case of a plausible association to previous infection we have post-infective aetiology. To be considered idiopathic, all this diagnostic assessment should be performed with a negative result, otherwise we should designate the patient as "not appropriately tested".

This aetiological algorithm was then applied to the ten databases previously mentioned, and results in terms of aetiology were compared.

A total of 2502 patients were accessed – 116 in Newcastle, 280 in Galway, 190 in Leuven, 113 in Serbia, 494 in Dundee, 88 in Haifa, 94 in Athens, 204 in Barcelona, 608 in Edinburgh and 315 in Monza. The median age was 64 years (age range – 18-97yr) with a majority of the population being over 65 years old (n=1404, 56.1%) and there was a female gender predominance (n=1539, 61.5%). Median Bronchiectasis Severity Index (BSI)(11) score was 7 with a relatively homogenous distribution between the severity groups – Mild (n=744, 29.7%), Moderate (n=894, 35.7%), Severe (n=864, 34.5%).

The global diagnosis made by clinicians and diagnosis after applying the algorithm, are presented on figure 1-B. A total of 1456 patients (58.2%) had an aetiological diagnosis made by the clinician. The most common aetiology, excluding idiopathic, was post-infective (n=427, 17.7%) and COPD (n=235, 9.4%).

After applying the aetiological algorithm, a significant reduction was seen in terms of idiopathic cases (n=1046, 41.8% vs n=726, 29.0%, $p<0.0001$). The number of patients with COPD as a BE aetiology was higher (n=373, 14.9%) and less post-infective cases were seen (n=349, 13.9%). A significantly higher number of GORD/aspiration cases were classified as probable aetiology – 109 cases (4.4%) versus only 15 cases (0.6%) considered by the clinicians. Moreover, CTD was also considered an aetiology more often – 237 cases (9.5%) versus 157 (6.3%) diagnosed by the clinicians.

These changes in aetiological classification were seen across all the centres. With the clinician diagnosis, we had 6 centres with more than 40% of idiopathic cases. That number went down to just one after applying the algorithm.

These results show that by applying the same structured aetiological algorithm to a bronchiectasis patient group the number of idiopathic cases can be lowered substantially. We demonstrate that clinicians frequently diagnose idiopathic bronchiectasis in the presence of disease associated with bronchiectasis suggesting the need for standardized aetiological categorization. This study has some limitations, even though centres practiced the BTS 2010 guideline testing algorithm, some testing particularly for CF, alpha-1 antitrypsin deficiency and PCD are still subject to "clinician suspicion" and so testing rates are highly variable between centres. In that matter, some of the patients considered as idiopathic could still be characterized as "not appropriately tested". In some cases, the algorithm can erroneously replace the diagnostic uncertainty of the clinician, because some elements are only present in a full clinical history and not recorded in the databases.

One of the major limitations is that the association between some diseases and bronchiectasis remains speculative. Particularly asthma and GORD are regarded as possible aetiologies but are very common in the general population and so cannot be regarded as definitive aetiologies. How to incorporate such diseases or phenotypes into classification algorithms is likely to require further discussion and debate over time.(12,13) The recently published European Bronchiectasis Guidelines recommended testing for immunodeficiency and ABPA routinely in all patients but did not address aetiological diagnosis in more detail. Therefore we believe our study is timely and may be incorporated into future guidelines.(14) The strengths of this study are the very large number of patients and that multiple and diverse bronchiectasis centres were included. Our study was limited to adults only and cannot be applied to children under the age of 18 years.

In summary, Idiopathic bronchiectasis should only be diagnosed after a thorough assessment with the exclusion of all the relevant clinical entities that could be related to bronchiectasis. The use of a standardized aetiological algorithm across all bronchiectasis centres, while imperfect, would improve the ability of reaching a diagnosis leading to a change in management in many cases and would enhance the ability to compare results of different studies from different centres.

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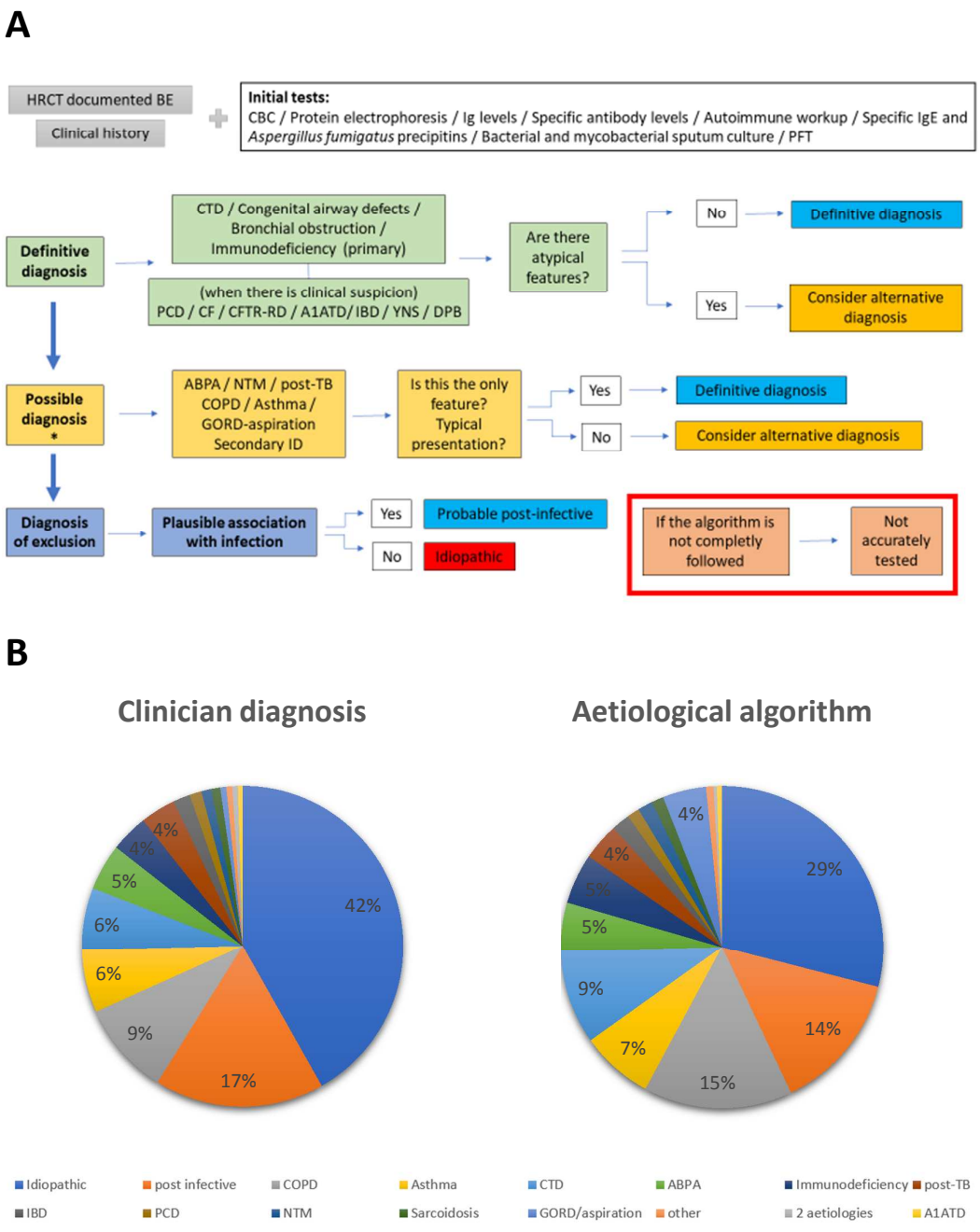

Figure 1 – A - Aetiology algorithm; B - Aetiology results, clinician diagnosis and results after aetiological algorithm. * note these diagnoses can also be complications or co-morbidities (e.g ABPA can complicate existing bronchiectasis)